REMARKS

Upon entry of this Reply, claims 1-32, 36, 37 and 44-48 will be pending and under active consideration. Applicants acknowledge the Examiner's statement regarding that DNA sequences disclosed in SEQ ID NOS:38, 40, 42, 44, 46, 48 and 50 and amino acid sequences disclosed in SEQ ID NOS:39, 41, 43, 45, 47, 49 and 51 are free of prior art.

Claims 35 and 38-43 have been canceled without prejudice, claims 1, 2, 4-14, 16, 17, 19-27, 34 and 36 have been amended, and claims 44-48 have been added to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Specifically, claims 35 and 38-43 have been canceled due to their withdrawal from consideration in view of a restriction requirement. Applicants reserve the right to prosecute the subject matter of these canceled claims in one or more related applications.

Claims 1, 2, 4-27, 34 and 36 have been amended. Specifically, claims 1 and 36 have been amended to recite that the isolated gene encodes a modified retinoblastoma tumor suppressor protein other than pRB^{94} or pRB^{56}, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not comprise a deletion of amino acids 1 through 378, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein. Claim 16 has also been amended to recite that the protein has a second insertion, substitution or deletion within the N-terminal 378 amino acids. Support for this amendment is found throughout the specification as filed, specifically, *inter alia*, at page 6, lines 28-30; page 7, line 6 to page 8, lines 26; and page 10, lines 25-30.

It is clear that the specification need not provide written description support in exactly the same words as are used in the claims. It is enough that the description conveys to one skilled in the art that the applicant had possession of the invention. For example, see *In re Wilder*, 736 F.2d 1516, 1520, 222 U.S.P.Q. 369, 372 (Fed. Cir. 1984):

> It is not necessary that the claimed subject matter be described identically, but the disclosure originally filed must convey to those skilled in the art that applicant has invented the subject matter later claimed.

See also *Application of Lukach*, 442 F.2d 967, 969, 169 U.S.P.Q. 795, 796 (C.C.P.A. 1971): "[T]he invention claimed does not have to be described in *ipsis verbis* in order to satisfy the

description requirement of § 112." The specification on page 6, lines 28-30; page 7, line 6 to page 8, lines 26; page 10, lines 25-30; page 11, lines 1-21; and page 80, lines 1-15 clearly conveys to one skilled in the art that the Applicant had possession of the claimed modified retinoblastoma tumor suppressor proteins having one or more insertions, substitutions or deletions within the N-terminal 378 amino acids of said protein.

Further, support for the proposition that claims can be properly amended or drafted to exclude a particular species of a genus can be found in In re Johnson, 194 U.S.P.Q. 187 (C.C.P.A. 1977). There the court considered the sufficiency under 35 U.S.C. § 112 of a specification in which a genus and several species were disclosed. The applicant claimed the genus while excluding two of the disclosed species in order to avoid the prior invention of another. The court reversed the decision of the Patent and Trademark Office Board of Appeals and held that an application which discloses a genus and several species provides sufficient support under Section 112 for claims excluding certain species in order to avoid a prior art rejection.

Claim 2 has been amended to recite that the gene encodes a modified retinoblastoma tumor suppressor protein in which at least one amino acid has been deleted from a first sequence region in the N-terminal 378 amino acids. Support for claim 2 as amended is found in the specification at page 7, lines 6-24. Claim 10 has been amended to recite that the modified retinoblastoma suppressor protein has at least one amino acid deletion in a second sequence region different from the first sequence region. Support for amended claim 10 is found at page 10, lines 25-27 and page 11, lines 13-14. Claim 19 has been amended to recite that the gene encodes a protein in which at least one amino acid has been deleted, and in which at least one amino acid has been substituted. Support for the amendment to claim 19 is found on page 11, lines 18-21 of the specification as filed.

Claims 4-9, 11, 12, 20 have been amended to delete the term "about". Claims 14 and 17 have been amended to point out that the mutation is a substitution. Claims 21 and 22 have been amended to state that the protein consists of the recited amino acid sequences or the recited nucleic acid sequences, respectively. Claims 13 and 23-27 have been amended in a non-substantiative manner to make the claims more clear. Claim 34 has been amended to recite that the gene encodes a modified retinoblastoma tumor suppressor protein: a) comprising at least one amino acid deletion in the N-terminal 378 amino acids, and wherein said modified retinoblastoma tumor suppressor protein has a biological activity at least

equivalent to the biological activity of the corresponding wild-type retinoblastoma tumor suppressor protein; or b) comprising at least one insertion or substitution in the N-terminal 378 amino acids, and wherein said modified retinoblastoma tumor suppressor protein has an increased biological activity in comparison to the biological activity of the corresponding wild-type retinoblastoma tumor suppressor protein. Support for claim 34 is found in the specification at page 6, lines 28-30; page 7, line 6 to page 8, lines 26; and page 15, lines 15-25.

New claims 44-48 have been added. Support for the new claims 44 and 45 is found in the specification at page 13, line 24 to page 14, line 6. New claim 46 is support in the specification at page 14, lines 8-15. New claims 47 and 48 are supported in the specification at page 15, lines 10-13.

No new matter is added by the amendments to the claims.

1. REJECTION UNDER 35 U.S.C. § 101

Claims 27-32 are rejected under 35 U.S.C. § 101, allegedly, because the claimed invention is directed to non-statutory subject matter. The Examiner alleges that the instantly claimed invention reads on host cells that have a DNA segment that may encode a naturally occurring mutant of Rb.

In response, Applicants have amended claim 27 to recite that the DNA segment is recombinantly transformed into the host cell. Claims 28-32 depend either directly or indirectly from claim 27. In view of the amendment to claim 27, Applicants submit that claims 27-32 are directed to statutory subject matter, and thus, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 101.

2. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

A. Claims 1-19, 23-32, 34, 36 and 37 are rejected under 35 U.S.C. § 112, first paragraph, allegedly, since the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention. According to the Examiner:

> the specification, while being enabling for DNA segments disclosed in SEQ ID NOS:28, 30, 32, 34, 36, 38, 40, 42,44, 46, 48, and 50 that encode mutant RB proteins (other than pRB94) that have deletions of 2-34, 2-55, 2-78, 2-97, 31-107, 77-107, 111/112, 111-181, 111-241, 181-241, 242-300 (disclosed in Seq ID 29,31,33, 35, 37, 39,41, 43,45,47, 49, and 51), expression vectors

comprising said DNA, [and] host cells comprising said DNA, [do] not reasonably provide enablement for any and all DNA segments that encode any and all mutants of RB wherein any 1, 2, 25,100, 150, 300 amino acids of the N-terminal 1-300 amino acids in one or two sequence regions of the N-terminus have been deleted, expression vectors comprising said mutant DNA segments and host cells comprising said DNA segments.

Applicants respectfully disagree. Preliminarily, Applicants point out that claim 1 has been amended to recite a DNA segment comprising an isolated gene encoding a modified retinoblastoma tumor suppressor protein other than pRB^{94} or pRB^{56}, in which said modified retinoblastoma tumor suppressor protein comprises an insertion, substitution or deletion within the N-terminal 378 amino acids of said protein, with the proviso that said modified protein does not comprise a deletion of amino acids 1 through 378, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein.

Applicants invite the Examiner's attention to the specification at page 6, line 9 to page 14, line 6 which describes the modified retinoblastoma proteins of the invention and page 77, line 23 to page 81, line 16 of the specification wherein the production of a number of exemplary modified retinoblastoma proteins of the present invention are produced. Moreover, the specification at page 81, line 18 to page 83, line 19 describes the characterization of the biological activity of such exemplary modified retinoblastoma proteins. As admitted by the Examiner, one of skill in the art could produce any of the disclosed modified retinoblastoma proteins. Moreover, Applicants submit that it is well within the skill of the skilled artisan to determine the biological activity of the modified retinoblastoma protein.

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original).

Applicants respectfully submit that it is not undue experimentation to produce the modified retinoblastoma proteins of the present invention and determine whether the produced protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein.

With regard to the Examiner's comment that equivalent biological activity is relative term and can be looked at differently, Applicants point out that the biological activities of retinoblastoma are well known to those of skill in the art, as are the methods for determining whether a modified retinoblastoma protein has a biological activity as compared to the corresponding wild type protein. Applicants invite the Examiner's attention to page 21, line 7 to page 27, line 20 wherein retinoblastoma protein and its biological activities are discussed. The Examiner's attention is also invited to the specification at page 44, line 25 to page 45, line 21 where biological functional equivalents are discussed.

With regard to the Examiner's comment as to the use of human cells that have a non-functional mutant of retinoblastoma, Applicants point out that the modified retinoblastoma protein encoded by the claimed nucleic acids has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein.

In view of the above amendments and remarks, it is submitted that the specification provides sufficient teaching to allow one skilled in the art to successfully make and use the claimed nucleic acids encoding a modified retinoblastoma tumor suppressor

protein, without undue experimentation. This rejection under Section 112, first paragraph, therefore, should be withdrawn.

B. Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner alleges that the specification as filed is not enabling for gene therapy because the art of gene therapy is highly unpredictable. Applicants respectfully disagree.

Under 35 U.S.C. § 112, a patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent and Trademark Office provides sufficient reason to doubt the accuracy of the disclosure. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 U.S.P.Q. 367, 369-70 (CCPA 1971). The claimed invention disclosed in the specification cannot be questioned on the unsupported skepticism of the Examiner. *Ex parte Linn*, 123 U.S.P.Q. 262 (PTO Bd. Pt. App. Int. 1959); *Ex parte Rosenwald*, 123 U.S.P.Q. 261 (PTO Bd. Pt. App. Int. 1959) (emphasis added). The number and variety of examples is irrelevant if the disclosure is "enabling" and set forth the "best mode contemplated." There is no absolute statutory requirement for a working example if the disclosure is such that one skilled in the art can practice the claimed invention. *In re Borkowski et al.*, 164 U.S.P.Q. 642 (CCPA 1970) (emphasis added). Even in an unpredictable art, Section 112 does not require disclosure of a test of every species encompassed by the claims. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (CCPA 1976). An invention is enabled even though the disclosure may require some routine experimentation to practice the invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The fact that the required experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v A.B. Fortia*, 774 F.2d 1104, 227 U.S.P.Q. 428 (Fed. Cir. 1985). A considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to the experimentation. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988); *In re Jackson*, 217 USPQ 804, 807 (PTO Bd. Pt. App. Int. 1982) (emphasis added). Finally, the Examiner has the

burden of showing that the disclosure entails undue experimentation. *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. 214 (CCPA 1976) (emphasis added).

Here, the specification provides considerable guidance and direction to practice the claimed invention. The Examiner's attention is invited the specification at page 16, lines 11-18 which states:

> The invention also provides a recombinant host cell comprising a DNA segment comprising an isolated gene encoding a modified retinoblastoma tumor suppressor protein other than pRB^{94}, the modified retinoblastoma tumor suppressor protein comprising an N-terminal modification. In one aspect of the invention the host cell is a prokaryotic host cell. In another aspect of the invention the host cell is *E. coli*. In a further aspect of the invention the host cell is a eukaryotic host cell. In yet another aspect of the invention the host cell is a tumor cell. In still another aspect of the invention the DNA segment is introduced into the cell by means of a recombinant vector.

The specification also describes on page 21, line 7 to page 27, line 20 that retinoblastoma is a tumor suppressor gene and has tumor growth suppressive activity, and on page 30, line 1 to page 43, line 12 teaches recombinant vectors comprising nucleic acids encoding the modified retinoblastoma protein and methods for delivering the vector into host cells. Moreover, the specification at page 23, line 7 *et seq.* teaches pharmaceutical compositions and routes of administration of the compositions into an organism.

Further, the specification describes in detail in Examples 1 through 10 of the production of exemplary vectors encoding for a modified retinoblastoma protein and transformation of host cells with said vectors. Moreover, the specification in Example 11 describes how therapeutic administration of the vectors encoding for a modified retinoblastoma protein of the present invention into subjects with tumors can be performed. The specification clearly enables one of skill in the art to practice the full scope of the claimed methods.

An invention meets the standard for successful practice set by Section 112 unless the invention is "totally incapable of achieving a useful result." *Brooktree v. Advances Micro Devices*, 24 U.S.P.Q.2D 1401, 1412 (Fed. Cir. 1992). The Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, 1st paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the

specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents. 34 U.S.P.Q.2d at 1439.

The Federal Circuit emphatically reversed the Board's decision. First, it explained the legal standard for compliance with the relevant Section 112 requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, the *Brana* Court made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must the applicant provide rebuttal evidence.

Second, the Federal Circuit explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1441.

In the *Brana* situation, the Court found that the Patent and Trademark Office had not met its initial burden. Further, the Court held that even if the Patent and Trademark Office had met its burden, the evidence proffered was clearly sufficient to meet the statutory requirement. As explained by the Court:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.*Id.* at 1442 [quoting *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961)].

The Federal Circuit further reminded the Commissioner that testing for the full safety and effectiveness of a product is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the requirements for obtaining government approval to market a particular drug for consumption. *Id.* at 1442; *see*, *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994).

Undue experimentation is experimentation that would require a level of ingenuity beyond what is expected from one of ordinary skill in the field. *Fields v. Conover*, 170 U.S.P.Q. 276, 279 (C.C.P.A. 1971). The factors that can be considered in determining

whether an amount of experimentation is undue have been listed in *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Among these factors are: the amount of effort involved, the guidance provided by the specification, the presence of working examples, the amount of pertinent literature and the level of skill in the art. The test for undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. *Id.*

While the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 U.S.P.Q. 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original).

In view of the above amendments and remarks, it is submitted that the specification provides sufficient teaching to allow one skilled in the art to successfully make and use the claimed recombinant host cells expressing a modified retinoblastoma tumor suppressor protein, without undue experimentation. This rejection under Section 112, first paragraph, therefore, should be withdrawn.

3. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 2-12, 20 and 34 are rejected under 35 U.S.C. § 112, second paragraph, allegedly, as indefinite for failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, claim 2 and dependent claims are allegedly vague and indefinite for reciting the term "about". In response, Applicants have amended the claims in all instances to delete the term "about", thus obviating this Section 112 rejection.

Further, claim 34 is allegedly vague and indefinite as it is unclear as to what would be considered "at least about biological activity". In response, and consistent with the response to the above-rejection, Applicants have amended claim 34 to delete the term "about".

Also, claim 10 is allegedly vague and unclear because it is unclear what would be considered a first sequence region and a second sequence region. In response, Applicants have amended claim 10 to recite that at least one amino acid has been deleted from said modified retinoblastoma tumor suppressor protein in a second sequence region different from the first sequence region. Applicants submit that it is clear that the second sequence region is defined as a region different from the first sequence region, which first sequence region is fully described in the specification.

In view of the foregoing, Applicants submit that the Section 112, second paragraph, rejections have been obviated, and thus, respectfully request their withdrawal.

4. REJECTIONS UNDER 35 U.S.C. § 102

A. Claims 1-7, 13, 20, 23, 24 and 27-30 are rejected under 35 U.S.C. 102(b), allegedly, as anticipated by Ewen et al., 1993, Cell 73:487-497 ("Ewen"). According to the Examiner, the invention of claims 1-7, 13, 20, 23, 24 and 27-30 is anticipated by Ewen since Ewen discloses a deletion mutant of retinoblastoma, in which amino acids 1 through 373 are deleted (called Large Pocket).

Applicants respectfully disagree with the Examiner. The present invention is directed to modified retinoblastoma proteins, and their encoding nucleic acids, which have an insertion, substitution or deletion within the N-terminal 378 amino acids, with the proviso that said modified protein does not comprise a deletion of amino acids 1 through 378, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein. Ewen discloses several modified retinoblastoma proteins, *e.g.*, the large pocket deletion mutant, which consists of amino acids 379 to 928, the small pocket deletion mutant, which consists of amino acids 373-936, a point mutation at amino acid position 706 and combinations of the point mutant and the deletion mutants.

In order for a reference to anticipate a claim, each and every element of the claim must be disclosed in that one reference. Orthokinetics, Inc. v. Safety Travel Chairs,

Inc., 806 F.2d 1565 (Fed. Cir. 1985). "Anticipation under Section 102 can be found only if a reference shows exactly what is claimed . . ." Structural Rubber Prod. Co. v. Park Rubber Co., 749 F.2d 707 (Fed. Cir. 1984). Ewen cannot and does not anticipate the claimed nucleic and amino acid sequences since Ewen does not teach a modified retinoblastoma protein, and its encoding nucleic acids, which has an insertion, substitution or deletion within the N-terminal 378 amino acids, with the proviso that said modified protein does not comprise a deletion of amino acids 1 through 378, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein.

With regard to the Examiner's comments that the retinoblastoma deletion mutant taught by Ewen has higher biological activity compared to wild type, Applicants invite the Examiner to Table 1 on page 491 of Ewen. The data in Table 1 clearly demonstrates that, contrary to the Examiner's assertion, the large pocket deletion mutant has less biological activity than wild type. Full length retinoblastoma ("Full-length Rb") was able to suppress the growth of cells such that an average of 31 colonies were counted in Experiment 1. The large pocket deletion mutant ("Rb large pocket") was only able to suppress the growth of cells such that an average of 63 colonies were counted. The two constructs were not compared in Experiment 2. Thus, the large pocket deletion mutant does not have a higher growth suppressive effect, as compared to the corresponding wild type protein.

Applicants respectfully submit that Ewen does not anticipate the claimed invention, and thus, withdrawal of this Section 102 rejection is respectfully requested.

B. Claims 1-7, 13, 20, 23, 24 and 27-30 are rejected under 35 U.S.C. 102(a), allegedly, as anticipated by Antelman et al., 1997, Oncogene 15:2855-2866 ("Antelman"). According to the Examiner, Antelman discloses a retinoblastoma mutant, in which N-terminal amino acids have been deleted to produce pRB^{56}. Applicants respectfully disagree and point out that the presently pending claims, as amended, explicitly exclude pRB^{56}. Moreover, pRB^{56}, as compared to wild type retinoblastoma, has amino acids 1-379 deleted. The claimed subject matter is directed, *inter alia*, to a modified retinoblastoma protein, or encoding nucleic acids thereof, in which the modified protein has an insertion, substitution or deletion within the N-terminal 378 amino acids, with the proviso that said modified protein does not comprise a deletion of amino acids 1 through 378. Thus, none of the claimed

subject matter is directed to pRB^{56}, and thus, none of the claimed subject matter is anticipated by Antelman. In view of the foregoing, Applicants respectfully request that this Section 102 rejection be withdrawn.

C. Claims 21 and 22 are rejected under 35 U.S.C. 102(b), allegedly, as anticipated by European Patent Publication EP 0 259 031 to Dryja et al., published March 9, 1988 ("Dryja"). According to the Examiner, Dryja discloses a human retinoblastoma protein having an amino acid sequence identical to SEQ ID NO:37 and which is encoded by a nucleic acid sequence that has 100% sequence identity to SEQ ID NO:36.

Applicants disagree and point out that claims 21 and 22 have been amended to recite that the encoded protein consists of the amino acid sequences of the recited SEQ ID NOS, and that the gene consists of the nucleotide sequences of the recited SEQ ID NOS, respectfully.

Dryja teaches a retinoblastoma protein in which the first 112 amino acids have been deleted as compared to wild type retinoblastoma, called pRB^{94}. None of the claimed subject matter is directed to pRB^{94} or to nucleic acids encoding pRB^{94}. Applicants point out that the amino acid sequence of SEQ ID NO:37 is a deletion of amino acids 1-147 as compared to wild type. Moreover, Applicants point out that the claimed subject matter specifically excludes pRB^{94}. In view of the foregoing, Applicants submit that Dryja does not anticipate the presently claimed subject matter, and thus, this Section 102 rejection should be withdrawn.

D. Claims 21 and 22 are rejected under 35 U.S.C. 102(b), allegedly, as anticipated by U.S. Patent No. 5,496,731 issued March 5, 1996 to Xu et al ("Xu"). According to the Examiner, Xu teaches retinoblastoma genes and gene products, in which sequence 1 of Xu "in the region 124-2466 has 100 percent query match as well as percent identity with the sequence disclosed in SEQ ID NO:36 (see sequence comparison with Accession No 118496 in the cited patent)". The Examiner also alleges that this region of sequence also encodes a protein that has 100 percent sequence similarity and identity with the sequence disclosed in SEQ ID NO:37 (see sequence comparison with Accession No 118496 in the cited patent).

Applicants respectfully disagree. As pointed out above, claims 21 and 22 have been amended to recite that the encoded protein consists of the amino acid sequences of the recited SEQ ID NOS, and that the gene consists of the nucleotide sequences of the recited SEQ ID NOS, respectfully. Xu teaches a retinoblastoma protein in which the first 112 amino

acids have been deleted as compared to wild type retinoblastoma, called pRB^{94}. None of the claimed subject matter is directed to pRB^{94} or to nucleic acids encoding pRB^{94}, and the claim language explicitly excludes pRB^{94}. In view of the foregoing, Applicants submit that Xu does not anticipate the presently claimed subject matter, and thus, this Section 102 rejection should be withdrawn.

In conclusion, Applicants respectfully submit that none of the cited references anticipates the presently claimed subject matter. Therefore, Applicants respectfully request that the Section 102 rejections be withdrawn.

5. REJECTIONS UNDER 35 U.S.C. § 103

A. Claims 21 and 22 are rejected under 35 U.S.C. 103(a), allegedly, as obvious over European Patent Publication EP 0 259 031 to Dryja et al., published March 9, 1988 ("Dryja"). According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention was made to modify the DNA sequence of Dryja by including a methionine codon at the beginning of nucleotides 166-2784, 234-2784, and 292-2784 of the nucleic acid sequence disclosed by Dryja to make the sequences disclosed in SEQ ID NOS:30, 32 and 34, respectively, with reasonable expectation of success because it is well recognized in the prior art that one requires ATG as the initiation codon that encodes for methionine for translating a DNA sequence into protein and without this codon translation will not be initiated.

Applicants respectfully disagree and point out that claims 21 and 22 have been amended to recite that the encoded protein consists of the amino acid sequences of the recited SEQ ID NOS, and that the gene consists of the nucleotide sequences of the recited SEQ ID NOS, respectfully. Dryja discloses a retinoblastoma protein which is missing the N-terminal 112 amino acids as compared to wild type retinoblastoma, as discussed above. In addition, Applicants point out that Dryja does not express the predicted protein using the disclosed nucleic acid sequence, and thus, Dryja did not determine whether the truncated retinoblastoma protein has biological activity equivalent to the biological activity of the corresponding retinoblastoma protein.

A rejection for obviousness is improper when there is nothing in the cited prior art references, either singly or in combination, to suggest the desirability of the claimed subject matter. For a rejection of claimed subject matter as obvious in view of a combination

of prior art references to be upheld, (1) the prior art must have suggested to those of ordinary skill in the art that they should make the claimed composition or device or use the claimed method, as the case may be; and (2) the prior art must have revealed that in so doing, those of ordinary skill would have had a reasonable expectation of success. In re Vaeck, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991); In re Dow Chemical Co., 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Dryja does not render obvious the claimed subject matter of claims 21 and 22 since one of ordinary skill upon reading Dryja would have found no motivation or suggestion to produce nucleic acids encoding a modified retinoblastoma protein, which modified retinoblastoma protein has a biological activity at least equivalent to the biological activity of the corresponding wild type retinoblastoma protein, and wherein the encoded modified protein consists of the contiguous amino acid sequence of SEQ ID NO:29; SEQ ID NO:31; SEQ ID NO:33; SEQ ID NO:35; SEQ ID NO:37; SEQ ID NO:39; SEQ ID NO:41; SEQ ID NO:43; SEQ ID NO:45; SEQ ID NO:47; SEQ ID NO:49; or SEQ ID NO:51 (claim 21), and that the gene consists of the contiguous nucleic acid sequence from between position 7 and position 2691 of SEQ ID NO:28; from between position 7 and position 2628 of SEQ ID NO:30; from between position 7 and position 2559 of SEQ ID NO:32; from between position 7 and position 2502 of SEQ ID NO:34; from between position 7 and position 2349 of SEQ ID NO:36; from between position 7 and position 2559 of SEQ ID NO:38; from between position 7 and position 2697 of SEQ ID NO:40; from between position 7 and position 2583 of SEQ ID NO:42; from between position 7 and position 2397 of SEQ ID NO:44; from between position 7 and position 2613 of SEQ ID NO:46; from between position 7 and position 2619 of SEQ ID NO:48; or from between position 7 and position 2790 of SEQ ID NO:50 (claim 22), respectfully.

Applicants believe that the Examiner is using the disclosure of the present invention as the suggestion to modify the retinoblastoma gene within the N-terminal 378 amino acids. "There must be a reason or suggestion in the art for reflecting the procedure used, other than knowledge learned from the applicant's disclosure." *In re Dow Chemical Co.*, 5 USPQ2d (Fed. Cir. 1988). Applicants, therefore, respectfully submit that the Examiner has not met his burden in setting forth a *prima facie* case of obviousness and as such the rejection, based on 35 U.S.C. §103 for obviousness, should be withdrawn.

B. Claims 21 and 22 are rejected under 35 U.S.C. 103(a), allegedly, as obvious over Friend et al., 1987, Proc. Natl. Acad. Sci. USA 84:9059-9063 ("Friend"). According to

the Examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the DNA sequence disclosed by Friend by including a methionine codon at the beginning of nucleotides 105-3057 of the sequence of Friend to make the sequences disclosed in SEQ ID NO:28 with a reasonable expectation of success because it is well recognized in the prior art that one requires ATG as the initiation codon that encodes for methionine for translating a DNA sequence into protein and without this codon translation will not be initiated.

Applicants respectfully disagree. As pointed out above, claims 21 and 22 have been amended to recite that the encoded protein consists of the amino acid sequences of the recited SEQ ID NOS, and that the gene consists of the nucleotide sequences of the recited SEQ ID NOS, respectfully. Friend teaches deletion of DNA sequences in retinoblastomas and mesenchymal tumors, which sequences correspond to the retinoblastoma gene locus.

Applicants respectfully submit that Friend does not render obvious the claimed subject matter of claims 21 and 22 since one of ordinary skill upon reading Friend would have found no motivation or suggestion to produce the claimed amino and nucleic acid sequences of claims 21 and 22, respectively.

Applicants believe that the Examiner is using the disclosure of the present invention as the suggestion to modify the retinoblastoma gene within the N-terminal 378 amino acids. Applicants, therefore, respectfully submit that the Examiner has not met his burden in setting forth a *prima facie* case of obviousness and as such the rejection, based on 35 U.S.C. §103 for obviousness, should be withdrawn.

In view of the foregoing, Applicants submit that none of the cited references, either alone or in combination, renders obvious the claimed subject matter, and thus, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the file of the above-identified patent application. Claims 1-32, 36, 37 and 44-48 fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections, allowance and action for issuance are respectfully requested.

Applicants respectfully request that the Examiner call the undersigned at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

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Enclosures